Effects of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Contrast-Induced Nephropathy

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Key Words
Contrast-induced nephropathy • Angiotensin-converting enzyme inhibitors • Angiotensin receptor blockers

Abstract
Contrast-induced nephropathy (CIN) is considered the third leading cause of iatrogenic acute kidney injury in high-risk patients undergoing radiographic procedures. The main mechanism leading to CIN is medullary hypoxia due to decreased renal blood flow, secondary to renal artery vasoconstriction and direct tubular toxicity by contrast medium. Furthermore, experimental data suggests that an activated renin–angiotensin–aldosterone system (RAAS) plays a role in the pathophysiology of CIN. However, the role of RAAS blockers, including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in CIN is controversial. They have been reported to be effective in the prevention of CIN in previous studies, but some studies have concluded that they were associated with an increased risk of CIN, especially in patients with pre-existing renal impairment. In summary, there is no solid data to link ACE inhibitors and ARB to CIN, and larger randomised controlled trials are necessary to further investigate their role in the development of CIN. In this review, we discuss the pathophysiology of CIN, the role of RAAS on the development of CIN, and the effect of RAAS blockers on CIN.

Introduction
With the increasing use of iodinated contrast media (CM) for diagnostic and interventional procedures, nephropathy induced by CM has become the third leading cause of hospital-acquired acute renal failure, accounting for 11% of cases [1, 2]. Contrast-induced nephropathy (CIN) is currently defined as an increase in serum creatinine concentration...
greater than 25% or 0.5 mg/dL (44 μmol/L) within 3 days of CM administration in the absence of an alternative cause [3]. The incidence of CIN is usually <2% in patients who do not have any risk factor for CIN, but it can rise up to 50% or more in patients with multiple risk factors [4]. Patients with pre-existing decreased kidney function, diabetes mellitus, congestive heart failure, old age, anaemia, decreased intravascular volume, recent acute myocardial infarction, or cardiogenic shock as well as those who receive a high volume of contrast media have increased risk of developing CIN [5, 6]. CIN may incur the need for dialysis, a prolonged hospital stay, a potentially irreversible reduction in renal function, and death.

Of all CIN prevention strategies investigated to date, including intravenous administration of fenoldopam or dobutamine, forced diuresis with diuretics or mannitol, and post-procedure hemodialysis, only periprocedural isotonic fluids given intravenously and avoidance of concurrent exposure to nephrotoxic agents has consistently resulted in renoprotection [7]. The role of renin-angiotensin-aldosterone system (RAAS)-blocking agents, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), in the pathophysiology of CIN is controversial because the available literature is conflicting [8-11]. Although several reports have suggested that these RAAS-blocking agents are nephrotoxic and worsen kidney failure in CIN [12], other reports have asserted that they protect the kidneys from the effects of CIN [13]. In this context, we review the medical literature and discuss the pathophysiology of CIN, the role of the RAAS on the development of CIN and the role of pharmacologic RAAS blockade in CIN.

Pathophysiology of CIN

The pathophysiology of contrast-induced nephropathy is not completely understood and is most likely multifactorial. The primary mechanisms underlying CIN include regional hypoxia due to changes in renal haemodynamics, direct cytotoxic effects to the renal tubular epithelium, and altered osmolar and viscous properties that affect renal haemodynamics and tubulodynamics. All of these mechanisms may act in concert. However, the importances of the mechanisms vary with the CM used, the type and degree of pre-existing individual risk factors, and the patient’s hydration status.

The influence of contrast media on renal haemodynamics may play a major role in the pathogenesis of CIN [14, 15]. The outer medulla is especially vulnerable to hypoxia: oxygen requirements are high due to salt reabsorption in Henle’s thick ascending limbs, but oxygen delivery is sparse. Low oxygen supply to the outer medulla is due to the great distance between the descending vasa recta that supply the medulla with blood. Moreover, arteriovenous shunt diffusion results in very low oxygen tension. Contrast media in the medulla affects the fragile balance between oxygen delivery and oxygen consumption through several mechanisms; the main mechanism is reduced blood perfusion. Medullary hypoperfusion relies on increased resistance to blood flow, due to, descending vasa recta vasoconstriction, among other factors. In both the cortex and the medulla, CM can shift the balance between vasodilatory and vasoconstrictive factors towards vasoconstriction [16, 17]. Because medullary perfusion comprises <10% of total renal blood flow, the vasoconstrictive response of total renal blood flow to CM observed in several studies reflects cortical rather than medullary effects. The degree of medullary vasoconstriction may markedly differ from the cortex, as may the factors involved [15, 18, 19]. Cortical vasoconstriction, or more precisely, preglomerular vasoconstriction is one cause of CM-induced reduction in the glomerular filtration rate (GFR) [15]. Preglomerular constriction can also reduce medullary flow, as descending vasa recta emerge from efferent arterioles; however, GFR reduction tends to reduce oxygen demand due to the decreased workload of tubular reabsorption. Other factors that may decrease renal blood flow include increased viscosity of CM and increased erythrocyte aggregation induced by CM, which results in diminished oxygen delivery [20].
The Role of RAAS in CIN

Experimental data suggest that stimulation of the RAAS is an important contributor to the development of CIN.

According to Duan SB et al., Ang II might play a role in the renal tubular cell apoptosis of rats induced by contrast media, and Telmisartan protected the renal tissue from the nephrotoxicity induced by contrast media [21]. Larson et al. [22] have successfully induced acute renal failure in animal models by administration of a contrast media bolus, and they found that sodium depletion accentuated both the magnitude and duration of the vasoconstrictive phase of the renal blood flow response to the injection of contrast medium and that blockade of the intrarenal renin-angiotensin system shortened the duration of this response. In addition, there is evidence that iodixanol, a nonionic, dimeric contrast media, causes increased oxidative stress and decreased nitric oxide production in outer medullary descending vasa recta, with consequent constriction of the descending vasa recta and increased reactivity to angiotensin II [16]. Activation of RAAS could also cause vasoconstriction of the efferent glomerular arteriole while simultaneously increasing the ex novo synthesis of vasodilator prostaglandins resulting in nearly stable or slightly increased intrarenal resistance. An angiotensin II-induced contraction of the magnitude, observed by Sendeski et al. [23], might further aggravate or halt most of the medullary perfusion when superimposed on vessels that are already constricted by contrast media.

There are convincing data that RAAS is a major mediator of renal injury. RAAS, especially angiotensin II, contributes to kidney injury through the angiotensin II type 1 receptor, transforming the growth factor-beta receptor, Smad and the epidermal growth factor receptor by affecting general angiostasis and vascular remodeling. This indirectly modulates inflammation and cellular reactions [24], and its proinflammatory action can lead to the upregulation of chemokines, adhesion molecules, and other fibrogenic growth factors that culminate in a decrease in renal function [25]. Furthermore, in a cohort of critically ill Caucasian patients, the ACE insertion genotype (ACE II) has been identified as a substantial risk factor in the development and outcome of acute kidney injury [26], including contrast-induced acute kidney injury. In addition, aldosterone, a steroid hormone, has been reported to be involved in renal injuries, including renal inflammation, oxidative stress, fibrosis, mesangial cell proliferation, and podocyte injury in various animal models, through the activation of the mineralocorticoid receptor [27, 28].

Effects of ACEI/ARB in CIN

Due to the increased use of RAAS blockade in patients with chronic kidney disease or cardiovascular disease, the potential role in the kidney is of increasing concern. Controversial results regarding the relationships of ACEI, ARB and CIN have been described in the literature [29]. Some studies have reported that RAAS blockers prevent CIN.

In a small in vivo study of the mechanisms of CIN, Russo et al. [30] demonstrated that a single dose of captopril or the calcium channel blocker nifedipine prior to exposure to contrast media could attenuate this decrease in GFR and renal plasma flow by 20% in patients with chronic kidney disease, hypothetically reducing the incidence of CIN. On a broader level and because of their intimate involvement with the RAAS, ACEIs have been hypothesised to decrease the incidence of CIN. Gupta et al. [31], in India, studied 71 randomised diabetic patients undergoing cardiac catheterisation with captopril 25 mg tid for 3 days (starting 1 h prior to procedure vs. no ACEI therapy), and the captopril group showed 79% reduced risk of developing CIN. It has been speculated that ACEIs may have a protective effect against CIN by counteracting the afferent arteriolar vasoconstriction and subsequent medullary ischemia induced by the activation of the RAAS after contrast administration [31]. In addition, Dangas et al. [13] illustrated a similar protective effect in patients with chronic kidney disease. These researchers retrospectively analysed more than 7,000 patients undergoing percutaneous
intervention and found that pre-procedural ACE inhibition reduced the risk of CIN in patients with chronic kidney disease.

In vitro studies that examined the cellular mechanisms of cellular stress and apoptosis have suggested a possible protective effect against CIN by ACEIs. Li XM et al. [32] reported 7 randomised controlled studies enrolling 792 patients undergoing intravascular angiography. They did not find clear evidence of an overall benefit from the use of ACEIs to prevent CIN. However, patients treated with ACEIs showed a lower mean creatinine level and a trend toward the reduced incidence of CIN compared with control patients. Although the conclusion from all published studies indicates that ACEIs may be effective in the prevention of CIN, this result is predominantly driven by findings from small, poor quality studies.

In contrast, the vast majority of studies have reported that RAAS blockers cause the deterioration of renal function. Hölscher et al. [33] prospectively assessed the predictors of CIN and the long-term outcomes of affected patients. Based on data from the 412 patients in the Dialysis-Versus-Diuresis trial, they determined that post-procedural hemodialysis, ACEI use, decreased baseline GFR, and the volume of contrast media administered were independently associated with the increased incidence of CIN. Toprak et al. [34] also showed that ACEIs (captopril) increased the incidence of CIN. Recently, several studies have reported that patients treated with RAAS inhibitors before exposure to contrast media show increased likelihood of developing contrast-induced acute kidney injury [12, 35-37].

The above studies were limited in their focus on patients with diabetes and patients with relatively normal kidney function. Other factors such as hypertension, prior renal disease, volume of contrast agent administered, congestive heart failure, were not taken into consideration in these early studies. Furthermore, ACEIs were given acutely, and the use of chronic ACEIs was not evaluated. The limitations of these studies were taken into consideration when Cirit et al. [38] performed a study evaluating chronic ACEI use as a risk factor for the development of CIN. Cirit et al. evaluated 230 patients with mild moderate renal insufficiency and randomised them into chronic ACEI users (taking an ACEI for at least 2 months) and those not taking an ACEI. The study results showed that 15.6% of the ACEI population and 5.8% of control population developed CIN. In the multivariate analysis, the risk factors for CIN included chronic ACEI, multi-vessel coronary involvement, diabetes mellitus, hypoaalbuminemia, a GFR<40 ml/min, and congestive heart failure. They postulated that the ACEI inhibition of RAAS leads to a decrease in glomerular hydrostatic pressure and thus glomerular filtration [39]. The decrease in glomerular filtration combined with the detrimental effects of contrast media in the kidneys likely resulted in the occurrence of CIN in this patient population. The Cirit et al. study addressed the question of whether to administer ACEIs prior to contrast exposure in order to decrease the risk of CIN. This question was further addressed by Rosenstock et al. [10] when they performed a large randomised prospective trial focused on determining whether discontinuation of ACEI therapy prior to angiography results in a withdrawal effect and an increase in the incidence of CIN. The authors found no statistically significant differences between the groups in the incidence of CIN: continuation group, 6.2%; discontinuation group, 3.7%; and naive group, 6.3% (P=0.66). Rosenstock et al. concluded that ACEIs do not increase the incidence of CIN and recommended not withholding ACEIs prior to contrast exposure. This conclusion is supported by a recent retrospective study of 178 patients with CKD who underwent coronary angiography. These authors reported that patients on RAAS blockade therapy before contrast exposure did not show increased incidence of CIN. There was also no increased incidence of CIN with ACE inhibitors or ARBs in the subgroups at higher risk, such as those with diabetes mellitus [40]. Recently a review has been published by Patel et al. [8]. In this review, the results of 5 randomised clinical trials and 678 patients were analysed. Based on these data, they also concluded that there is no definitive correlation between ACEIs and the occurrence of CIN in the cardiac catheterisation laboratory and that withholding ACEIs prior to catheterisation most likely does not decrease the incidence of CIN and is not recommended. They also stated that starting ACEIs before the procedure for the sole purpose of lowering the risk of CIN cannot be recommended based on the current evidence.
The effect of ARBs on CIN is also unclear. Spatz C et al. [40] performed a retrospective study of patients with CKD stages 3 and 4 who were either on or off RAAS blockade therapy at the time of coronary angiography. They found that patients with ARB therapy before contrast exposure did not show higher incidence of CIN. Another study found that withholding ARBs 24 h before coronary angiography did not influence the incidence of CIN in stable patients with chronic kidney disease in stages 3-4 [10]. Oguzhan N et al. performed a prospective study and concluded that amlodipine/valsartan therapy plus hydration did not reduce the risk of CIN in chronic kidney disease. Stage 2 patients who underwent elective coronary angiography using a low-osmolar nonionic contrast medium and recommended avoiding ARBs and calcium-channel blockers before coronary angiography in high-risk patients [41].

**Conclusion**

CIN is a known complication of iodinated contrast administration after angiography and interventions. The mechanisms remain unclear, but several identifiable risk factors increase the likelihood of developing CIN post-contrast exposure. This review focused on the role of RAAS in CIN. The data regarding ACEI/ARB and CIN are conflicting. Studies have reported a protective effect, while others have reported a negative effect or no effect. Based on the data, there is no definite correlation between ACEI/ARB and the occurrence of CIN post-contrast exposure in the cardiac catheterisation laboratory. Thus, withholding ACEI/ARB prior to catheterisation most likely does not decrease the incidence of CIN and is not recommended. Subsequently, starting ACEI/ARB before the procedure for the sole purpose of lowering the risk of CIN cannot be recommended based on the current evidence. Because the role of ACEI/ARB in CIN is paradoxical and considering that it is widely used in the clinic before CM administration, larger randomised controlled trials are urgently required to more thoroughly investigate the role of ACEI/ARB in the development of CIN.

**Conflicts of Interests**

The authors declare there are no conflicts of interest.

**Acknowledgements**

The work was supported by grants from the National Natural Science Foundation of China (No.81300567) and the Foundation of Science and technology department in Hunan Province (No. 2013FJ4072).

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